Maternal Hyperthyroidism: Impact on the pregnancy and the fetus

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Pregnancy as an event complicating primary Graves' disease occurred in about half the cases in which it was possible. . .The results were poor, for there was an unsuccessful termination by miscarriage or premature birth in about 50 per cent. . . . The result appears to depend on the severity of the disease at the time of pregnancy.

Gardner-Hill, Lancet 1929

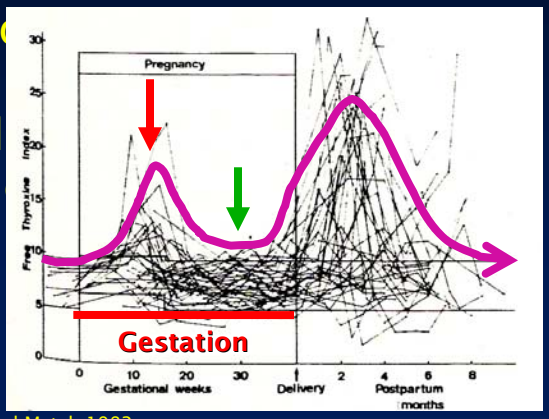
- Maternal hyperthyroidism
  - Graves' disease
  - Adverse outcomes for gestational physiology
- Antithyroid drugs
  - Maternal thyroid function
  - Fetal/neonatal thyroid funtion
- Optimizing maternal antithyroid therapy

Maternal hyperthyroidism: Diagnosis

- Graves' Disease
- Toxic nodule (s)
- Thyroiditis
- Hydatidiform mole
- [Gestational thyrotoxicosis]

Maternal hyperthyroidism: Diagnosis

- Graves' Disease 1:500-2000 pregnancies
- Toxic n
- Thyroid
- Hydatid
- [Gestati

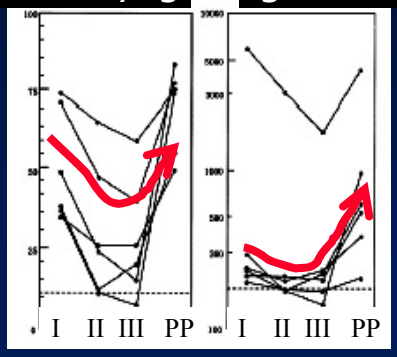


Amino, J Clin Endocrinol Metab 1982

Changes in TSH Receptor antibodies during gestation

Thyroid binding inhibitory Ig

Thyroid stimulating Ig



Amino, J Clin Endocrinol Metab, 2003

Graves' Disease (GD) In Pregnancy: various presentations

- Hyperthyroidism is diagnosed for the first time during pregnancy
- The patient is on antithyroid drugs (ATD) at the time of conception
- The patient is in remission and then relapses during pregnancy
- (The patient has undergone I-131 ablation or surgery AND is on thyroid hormone replacement, but produces TSH receptor antibodies)

Diagnosis of Hyperthyroidism in Pregnancy

- Total and free T4 and T3 levels above the normal ranges for pregnancy
  - TT4 and TT3 1.5 x nonpregnant range[1]
  - Free T4 -- trimester-specific[2]
- TSH below trimester-specific PREGNANT reference range
- Measurement of TSH receptor Ab (TRAb) rarely indicated
- PEx: goiter with bruit or thrill
- *Suppressed TSH and/or elevated free T4 may appear transiently in first trimester in ~18% of pregnancies[3]*

[1]http://www.nacb.org/lmpg/main.stm; [2]Spencer, ITA 2005; [3]Goodwin, Am J Obstet Gynecol 1992

Maternal hyperthyroidism: Adverse outcomes

- Retrospective studies, some predating TSH measurement
- Dx based upon clinical signs (↑HR, wt loss, lid lag) and protein-bound iodine or total T4
- ATD adjusted to "resting pulse", "weight gain", T4
- Analyses not adjusted for other comorbidities

Mestman, Arch Intern Med 1974; Davis, Am J Obstet Gynecol 1989; Millar, Obstet Gynecol 1994; Sugrue Br J Obstet Gynecol 1980

Pregnancy Complications: Gestational Outcome

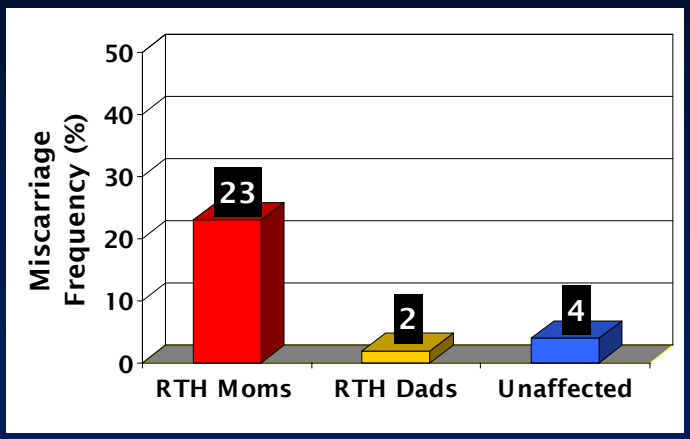
	Controlled on ATD Rx	Untreated
Miscarriage[1,5]	8-10%	21%
Pr[illegible][1,2,3]	[illegible]	[illegible]
Pr[illegible]	[illegible]	[illegible]
He[illegible]	[illegible]	[illegible]
Stillbirth[1,5]	0%	7-30%
Small for gestational age[4,5]	less	more
Thyroid storm	less	more

"The result appears to depend on the severity of the disease at the time of pregnancy." Gardner-Hill, 1929

[1]Mestman, Arch Intern Med 1974; [2]Davis, Am J Obstet Gynecol 1989; [3]Millar, Obstet Gynecol 1994; [4]Mitsuda Obstet Gynecol 1992; [5]Sugrue Br J Obstet Gynecol 1980

Fetal loss associated with excess in utero thyroid hormone exposure

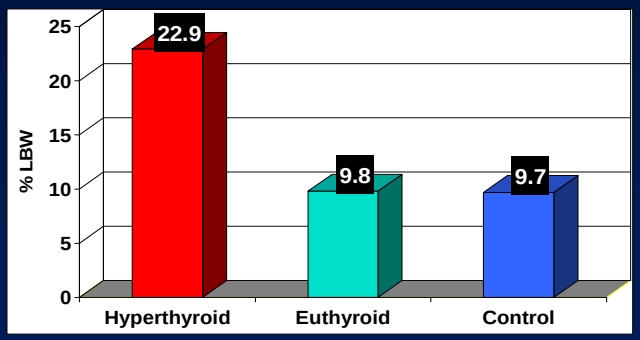
9 Moms and 9 Dads with Resistance to Thyroid Hormone→ 89 pregnancies



Anselmo, JAMA 2005

Can the risk of complications be decreased?

Risk of LBW (<2500gm) and 3rd trimester maternal thyroid status



Phoojaroenchanachai, Clin Endocrinol 2001

Antithyroid drugs

Is there a preferred antithyroid drug in pregnancy?

PTU vs. Methimazole (MMI)

- Transplacental passage?

Transplacental Passage: PTU vs. MMI

- In early pregnancy, after a single ^{35}S-PTU or ^{35}S-MMI injection in 9 women undergoing therapeutic abortions, the ratio of fetal to maternal serum levels was ~30% for PTU (2 women) whereas for MMI, it was ~80% (2 women).
- *"At present, there are insufficient data to decide whether methimazole or PTU would be preferable for the treatment of thyrotoxicosis in pregnancy"*

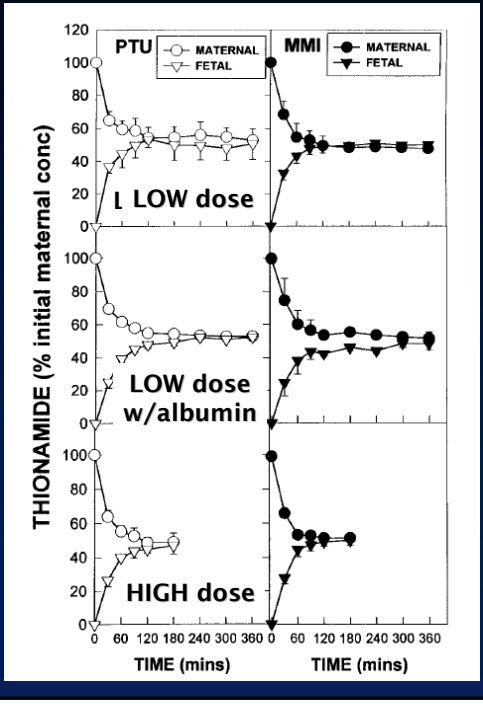
Marchant et al, J Clin Endocrinol Metab 1977; Gardner et al, J Clin Endocrinol Metab 1986

Transplacental Passage: PTU vs. MMI

- In early pregnancy, after a single ^{35}S-PTU or ^{35}S-MMI injection in 9 women undergoing therapeutic abortions, the ratio of fetal to maternal serum levels was ~30% for PTU (2 women) whereas for MMI, it was ~80% (2 women).
- At term, cord blood PTU levels were higher than maternal serum PTU levels in 5 women with Graves' women treated with 100-150mg tid of PTU.

Marchant et al, J Clin Endocrinol Metab 1977; Gardner et al, J Clin Endocrinol Metab 1986

PTU and MMI have similar placental transfer



Mortimer, J Clin Endocrinol Metab 1997

Is there a preferred antithyroid drug in pregnancy?
PTU vs. Methimazole

- Transplacental passage?
  - 1st trimester (?? methimazole > PTU)
  - Term (cord PTU levels higher than maternal)
- Teratogenic effects?
  - Methimazole (? aplasia cutis, embryopathy including choanal atresia, esophageal atresia, TE fistula, athelia)

Mandel et al, Thyroid 1994; Marchant et al, J Clin Endocrinol Metab 1977; Gardner et al, J Clin Endocrinol Metab 1986, Wilson Am J Med Genet 1998; DiGianantonio, Teratology 2001

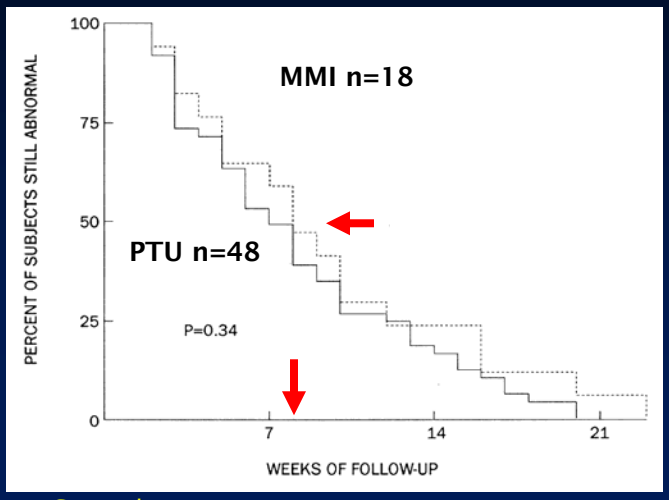
Congenital Malformations and Maternal Thyroid Status

Maternal Thyroid Status 1st Trimester	n	Congenital Malformations n (%)
Hyperthyroid	167	5 (36%)*
Untreated	50	3 (6%)
Treated (MMI)	117	2 (2%)
Euthyroid	476	1 (0.2%)*
Untreated	350	1 (0.3%)
Treated (MMI)	126	0 (0%)

Momotani, Clin Endorinol 1984

Antithyroid drugs: Maternal Thyroid Function

Time to Normalization of T4



Wing, Am J Obstet Gynecol

Antithyroid drugs: Neonatal Thyroid Function

Is there a correlation between maternal ATD dose and neonatal thyroid function?

Maternal Antithyroid Rx and Neonatal TFT's

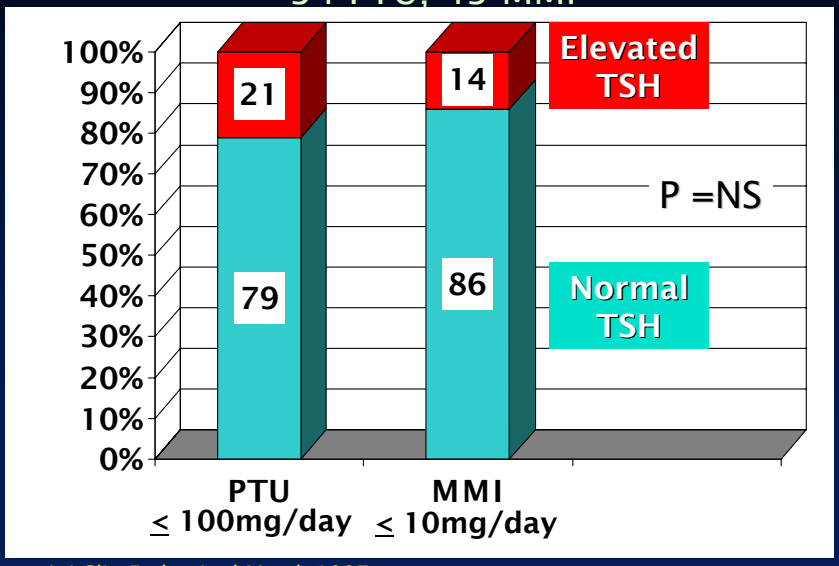
	No. of pregnancies	Antithyroid Rx
Dose Response		
Lamberg 1981	11	CM (Carbimazole)
Mortimer 1990	16	PTU or CM
Mitsuda 1992	230	MMI or PTU

Maternal Antithyroid Rx and Neonatal TFT's

	No. of pregnancies	Antithyroid Rx
Dose Response		
Lamberg 1981	11	CM (Carbimazole)
Mortimer 1990	16	PTU or CM
Mitsuda 1992	230	MMI or PTU
No Dose Response		
Cheron 1981	11	PTU
Gardner 1986	6	PTU
Momotani 1986	43	MMI or PTU
1997	77	MMI or PTU

Cord TSH levels

77 women with Graves'
34 PTU, 43 MMI



Momotani, J Clin Endocrinol Metab 1997

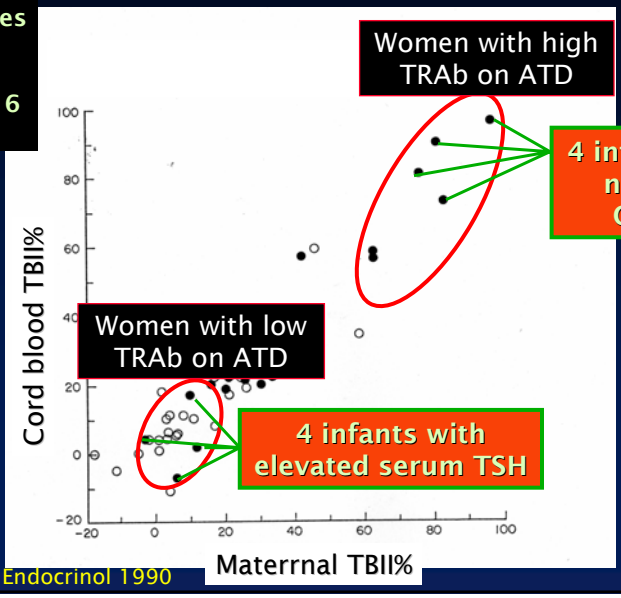
Fetal thyroid function reflects transplacental passage of two maternal factors:

- INHIBITORY:
  antithyroid drug concentration

- STIMULATING:
  TSH receptor antibody

Cord Blood and Maternal TSH Receptor Ab

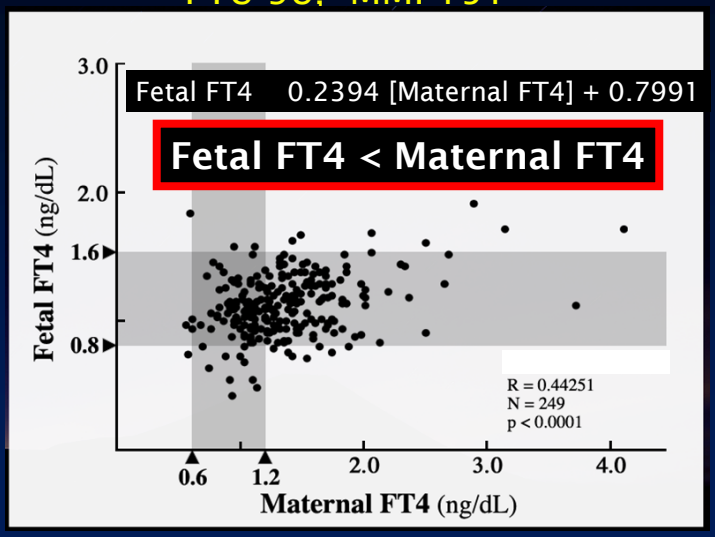
46 pregnancies
At term
No Rx-30
PTU or CM-16



Mortimer, Clin Endocrinol 1990

Correlation between Maternal and Fetal FT4

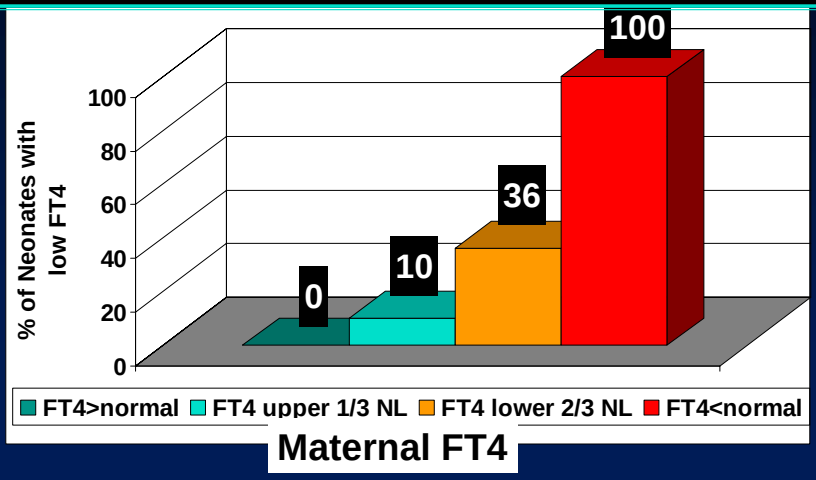
249 women with GD treated to term
PTU 98, MMI 151



Momotani, ATA 2006

Cord FT4 as a Function of Maternal FT4

If maternal FT4 1.9 -2.2ng/dl (24-28pmol/L) → neonatal TFTs normal[2]



Momotani, N Engl J Med 1986; [2]Momotani, ATA 2006

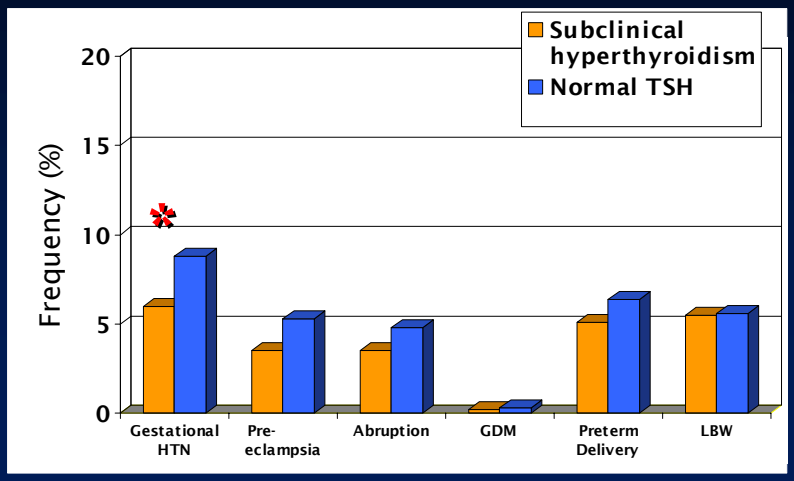
What "normal" FT4 levels in pregnancy?

- FT4 values decrease in the 3rd trimester
  - Using automated assays, the 95% CI is ~ 0.6 to 1.4 ng/dl[1]
- Momotani used a NONPREGNANT FT4 reference range of 1.0-1.8 ng/dl[2]
- So, in the 3rd trimester, we are in fact truly "undertreating" women with Graves' disease compared to normal pregnant physiology

[1]Sapin et al Clin Lab 2004; [2]Momotani et al, N Engl J Med 1986

No Adverse Outcome in SUBCLINICAL hyperthyroidism

433 women with TSH ≤ 2.5th %tile for gestational age and fT4 ≤ 1.75ng/dL



Casey, Obstet Gynecol 2006

Optimizing ATD therapy

Treatment Goal: SUBCLINICAL HYPERTHYROIDISM

- **2.1.a.2. For overt hyperthyroidism due to Graves' disease or hyperfunctioning thyroid nodules, antithyroid drug therapy should be either initiated (for those with new diagnoses) or adjusted (for those with a prior history) to maintain the maternal thyroid hormone levels for free T4 in the upper nonpregnant reference range. USPSTF Recommendation level-A**

Thyroid Dysfunction during Pregnancy and Postpartum Guidelines, Endocrine Society 2007

2.1.a.3. Because available evidence suggests methimazole may be associated with congenital anomalies, propylthiouracil should be used as a firstline drug, if available, especially during first trimester organogenesis. Methimazole may be prescribed if propylthiouracil is not available or if a patient cannot tolerate or has an adverse response to propylthiouracil. USPSTF recommendation level B

Thyroid Dysfunction during Pregnancy and Postpartum Guidelines, Endocrine Society 2007

In the US, should we reconsider?

- PTU during 1st trimester organogenesis
- MMI afterwards because of lower hepatotoxicity

As the dose of antithyroid drug used to restore the hypermetabolism of thyrotoxicosis to normal still permits the thyroid gland to form and secrete a normal amount of thyroid hormone, there is reason to suppose that the fetal thyroid would not be significantly suppressed by appropriate treatment of the thyrotoxic mother.

Astwood, J Clin Endocrinol 1951



Appropriate Treatment!!!

Optimizing therapy

Treatment Goal: SUBCLINICAL HYPERTHYROIDISM

Free T4: Use nonpregnant reference range
Keep at upper NL to 10% above

Total T4: Normal pregnancy range 1.5x non-pregnant range
Keep at upper NL to 10% above

TSH: May consider measuring TSH after 2-3 months, keep at or just below lower trimester-specific limit

http://www.nacb.org/lmpg/main.stm